(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 1 127 059 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
20.02.2008 Bulletin 2008/08

(21) Application number: **99953956.2**

(22) Date of filing: **29.10.1999**

(51) Int Cl.:
C07D 471/14 *(2006.01)* ***A61K 31/44*** *(2006.01)*

(86) International application number:
PCT/EP1999/008227

(87) International publication number:
WO 2000/026217 (11.05.2000 Gazette 2000/19)

(54) **IMIDAZONAPHTHYRIDINES**

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(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV MK RO SI

(30) Priority: **03.11.1998 EP 98120834**

(43) Date of publication of application:
29.08.2001 Bulletin 2001/35

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EP 1 127 059 B1

Printed by Jouve, 75001 PARIS (FR)

Description

Field of application of the invention

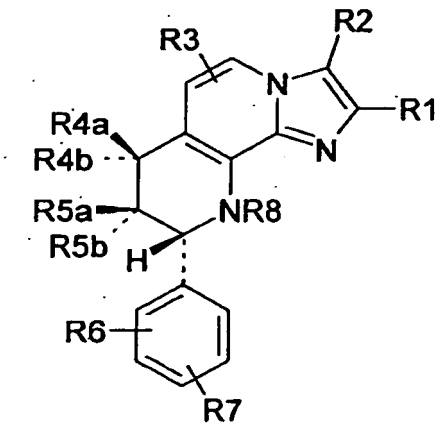
[0001] The invention relates to novel compounds which are used in the pharmaceuticals industry as active compounds for preparing medicaments.

Known technical background

[0002] US Patent 4,468,400 describes tricyclic imidazo[1,2-a]pyridines having different ring systems fused to the imidazopyridine skeleton, which compounds are said to be suitable for treating peptic ulcer disorders. The International Patent Application WO98/42707 discloses tetrahydroimidazonaphthyridines having a very particular substitution pattern, which compounds are likewise said to be suitable for treating gastrointestinal disorders.

Description of the invention

[0003] The invention provides compounds of the formula I



(I)

in which

R1 is 1-4C-alkyl,
R2 is 1-4C-alkyl,
R3 is hydrogen,

one of the substituents R4a and R4b is hydrogen and the other is R4',
where

R4' is $-O-(CH_2)_m-S(O)_n-R9$,

in which R9 is 1-4C-alkyl,

m is the number 2 or 3 and
n is the number 0, 1 or 2,

one of the substituents R5a and R5b is hydrogen and the other is hydroxyl,

R6 is hydrogen,
R7 is hydrogen and
R8 is hydrogen,

and their salts.

[0004] 1-4C-Alkyl represents straight-chain or branched alkyl radicals having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

[0005] Suitable salts of compounds of the formula I are - depending on the substitution - in particular all acid addition salts. Particular mention may be made of the pharmacologically acceptable salts of the inorganic and organic acids customarily used in pharmacy. Those suitable are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, where the acids are employed in the salt preparation in an equimolar ratio or a ratio differing therefrom, depending on whether the acid is a mono- or polybasic acid and on which salt is desired.

[0006] Pharmacologically unacceptable salts, which can be initially obtained, for example, as process products in the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically acceptable salts by processes known to the person skilled in the art.

[0007] It is known to the person skilled in the art that the compounds according to the invention and their salts can, for example when they are isolated in crystalline form, comprise varying amounts of solvents. The invention therefore also embraces all solvates and, in particular, all hydrates of the compounds of the formula I, and all solvates and, in particular, all hydrates of the salts of the compounds of the formula I.

[0008] The compounds of the formula I have at least three chiral centers. The invention provides all eight feasible stereoisomers in any mixing ratio, including the pure enantiomers which are the preferred subject matter of the invention.

[0009] An exemplary preferred radical R1 is the methyl radical.

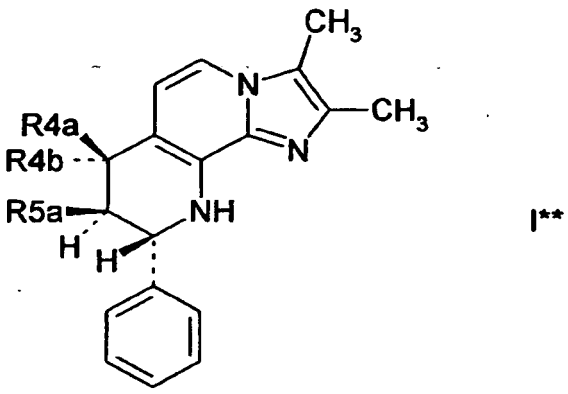
[0010] An exemplary preferred radicals R2 is the methyl radical.

[0011] Exemplary radicals R9 which may be mentioned are: methyl, ethyl, propyl, isopropyl, butyl and isobutyl.

[0012] Selected preferred compounds I are those in which R5b is hydrogen.

[0013] Selected particularly preferred compounds I are those in which R5b is hydrogen and R4a is hydrogen.

[0014] The following preferred compounds according to the invention selected by way of example may be mentioned specifically using formula I** below with the substituent definitions for R4a, R4b and R5a of Table 1 (Tab. 1) below:



I**

Tab. 1

R4a	R4b	R5a
H	$-OCH_2CH_2SCH_3$	-OH
H	$-OCH_2CH_2SOCH_3$	-OH
H	$-OCH_2CH_2SO_2CH_3$	-OH
$-OCH_2CH_2SCH_3$	H	-OH
$-OCH_2CH_2SOCH_3$	H	-OH
$-OCH_2CH_2SO_2CH_3$	H	-OH

[0015] The compounds according to the invention are prepared, for example, starting from the compounds of the

formula I known from WO98/42707 in which at least one of the substituents R4a, R4b, R5a and R5b is hydroxyl (referred to as "starting materials" hereinbelow). Starting with the starting materials, the compounds according to the invention can be prepared by various routes, depending on which end product is desired, for example by acid-catalyzed etherification of the starting materials with compounds of the formula R4'-H or R5'-H.

[0016] For the compounds of the formula I according to the invention in which n is different from the number 0, the reaction is followed by oxidation.

[0017] The oxidation of the sulfides to the sulfoxides or sulfones is carried out under the conditions known to the person skilled in the art for oxidizing sulfides to sulfoxides and sulfones respectively, [see, for example, J. Drabowicz and M. Mikolajczyk, Organic preparations and procedures int. 14(1-2), 45-89 (1982) or E. Block in S. Patai, The Chemistry of Functional Groups, Supplement E. Part 1, pp. 539-608, John Wiley and Sons (Interscience Publication), 1980]. Suitable oxidizing agents are all reagents which are customarily used for oxidizing sulfides to sulfoxides or sulfones.

[0018] Sulfoxides are optically active compounds, so that for n = 1, one or more further chiral centers are introduced into the molecule. With respect to the sulfoxides, the invention therefore also embraces both the enantiomers and diastereomers and their mixtures and racemates. The enantiomers can be separated in a manner known per se (for example by preparing and separating corresponding diastereoisomeric compounds).

[0019] The following examples illustrate the invention in more detail, without limiting it The compounds according to the invention can be prepared in a manner analogous to that described in the examples. The abbreviation RT stands for room temperature, h stands for hour(s), m.p. stands for melting point and decomp. stands for decomposition.

Examples

1. (7R,8R,9R)-2,3-dimethyl-8-hydroxy-7-(2-methylthioethyloxy)-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h][1,7]naphthyridine

[0020]

1. g of (7R,8R,9R)-7,8-dihydroxy-2,3-dimethyl-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h][1,7]-naphthyridine, dissolved in 30 ml of dioxane and 5 ml of dimethyl-formamide, is admixed with 0.63 g of concentrated sulfuric acid and 1 g of 2-methylmercaptoethanol. The mixture is stirred at RT for 3 h, poured into ice-water (200 ml), adjusted to pH 8 using 2 N aqueous sodium hydroxide solution and extracted three times with methylene chloride. The solvent is stripped off under reduced pressure and the oily residue that remains is purified on silica gel (mobile phase: diethyl ether). This gives 80 mg of the title compound of m.p. 118-9°C (diisopropyl ether).

2. (7S,8R,9R)-2,3-imethyl-8-hydroxy-7-(2-methylthioethyloxy)-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h][1,7]naphthyridine

[0021] The mother liquor from Example 1 gives, after purification on silica gel (mobile phase: diethyl ether), 40 mg of the title compound of m.p. 109-10°C.

3. (7R,8R,9R)-2,3-dimethyl-8-hydroxy-7-(2-methylsulphinylethoxy)-9-phenyl-7,8,9,10-tetrahydroimldazo[1,2-h][1,7]naphthyridine

[0022] 130 mg of sodium metaperiodate, dissolved in 1 ml of water, is added to a solution of 200 mg of (7R,8R,9R)-2,3-dimethyl-8-hydroxy-7-(2-methylthioethoxy)-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h]-[1,7]naphthyridine in 5 ml of methanol. After two hours stirring at room temperature, 50 ml of water are added. The mixture is extracted three times with dichloromethane, the organic phases are collectively washed with water and dried over sodium sulphate. The solvent is removed in vacuo and the remaining residue is purified by chromatography on silica gel (eluent: ethylacetate/methanol = 10/1). 100 mg of the title compound of m.p. 105 -106°C are obtained.

4. (7S,8R,9R)-2,3-dimethyl-8-hydroxy-7-(2-methylsulphinylethoxy)-9-phenyl-7,8,9,10-tetrahydroimidazo[1,2-h][1,7]naphthyridine

[0023] 80 mg of the title compound of m.p. 85 - 87°C are obtained by oxidation of 200 mg of (7S,8R,9R)-2,3-dimethyl-8-hydroxy-7-(2-methylthioethoxy)-9-phenyl-7,8,9,10-tetrahydro-imidazo[1,2-h][1,7]naphthyridine analogously to Example 3.

Commercial utility

[0024] The compounds of the formula I and their salts have valuable pharmacological properties which make them commercially utilizable. In particular, they exhibit marked inhibition of gastric acid secretion and an excellent gastric and intestinal protective action in warm-blooded animals, in particular humans. In this connection, the compounds according to the invention are distinguished by a high selectivity of action, an advantageous duration of action, a particularly good enteral activity, the absence of significant side effects and a large therapeutic range.

[0025] "Gastric and intestinal protection" in this connection is understood as meaning the prevention and treatment of gastrointestinal diseases, in particular of gastrointestinal inflammatory diseases and lesions (such as, for example, gastric ulcer, duodenal ulcer, gastritis, hyperacidic or medicament-related functional dyspepsia), which can be caused, for example, by microorganisms (e.g. Helicobacter pylon), bacterial toxins, medicaments (e.g. certain antiinflammatories and antirheumatics), chemicals (e.g. ethanol), gastric acid or stress situations.

[0026] In their excellent properties, the compounds according to the invention surprisingly prove to be clearly superior to the compounds known from the prior art in various models in which the antiulcerogenic and the antisecretory properties are determined. On account of these properties, the compounds of the formula I and their pharmacologically acceptable salts are outstandingly suitable for use in human and veterinary medicine, where they are used, in particular, for the treatment and/or prophylaxis of disorders of the stomach and/or intestine.

[0027] A further subject of the invention are therefore the compounds according to the invention for use in the treatment and/or prophylaxis of the abovementioned diseases.

[0028] The invention likewise includes the use of the compounds according to the invention for the production of medicaments which are employed for the treatment and/or prophylaxis of the abovementioned diseases.

[0029] The invention furthermore includes the use of the compounds according to the invention for preparing medicaments for the treatment and/or prophylaxis of the abovementioned diseases. A further subject of the invention are medicaments which comprise one or more compounds of the formula I and/or their pharmacologically acceptable salts.

[0030] The medicaments are prepared by processes which are known per se and familiar to the person skilled in the art. As medicaments, the pharmacologically active compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries or excipients in the form of tablets, coated tablets, capsules, suppositories, patches (e.g. as TTS), emulsions, suspensions or solutions, the active compound content advantageously being between 0.1 and 95% and it being possible to obtain a pharmaceutical administration form exactly adapted to the active compound and/or to the desired onset of action (e.g. a sustained-release form or an enteric form) by means of the appropriate selection of the auxiliaries and excipients.

[0031] The auxiliaries and excipients which are suitable for the desired pharmaceutical formulations are known to the person skilled in the art on the basis of his/her expert knowledge. In addition to solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active compound excipients, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, colorants or, in particular, permeation promoters and complexing agents (e.g. cyclodextrins).

[0032] The active compounds can be administered orally, parenterally or percutaneously.

[0033] In general, it has proven advantageous in human medicine to administer the active compound(s) in the case of oral administration in a daily dose of approximately 0.01 to approximately 20, preferably 0.05 to 5, in particular 0.1 to 1.5, mg/kg of body weight, if appropriate in the form of several, preferably 1 to 4, individual doses to achieve the desired result. In the case of a parenteral treatment, similar or (in particular in the case of the intravenous administration of the active compounds), as a rule, lower doses can be used. The establishment of the optimal dose and manner of administration of the active compounds necessary in each case can easily be carried out by any person skilled in the art on the basis of his/her expert knowledge.

[0034] If the compounds and/or their salts according to the invention are to be used for the treatment of the abovementioned diseases, the pharmaceutical preparations can also contain one or more pharmacologically active constituents of other groups of medicaments, for example: tranquilizers, (for example from the group of the benzodiazepines, for example diazepam), spasmolytics (for example, bietamiverine or camylofin), anticholinergics, (for example, oxyphencyclimine or phencarbamide), local anesthetics, (for example, tetracaine or procaine), and, if appropriate, also enzymes, vitamins or amino acids.

[0035] To be emphasized in this connection is in particular the combination of the compounds according to the invention with pharmaceuticals which inhibit acid secretion, such as, for example, H_2 blockers (e.g. cimetidine, ranitidine), H^+/K^+ ATPase inhibitors (e.g. omeprazole, pantoprazole), or further with so-called peripheral anticholinergics (e.g. pirenzepine, telenzepine) and with gastrin antagonists with the aim of increasing the principal action in an additive or super-additive sense and/or of eliminating or of decreasing the side effects, or further the combination with antibacterially active substances (such as, for example, cephalosporins, tetracyclines, penicillins, macrolides, nitroimidazoles or alternatively bismuth salts) for the control of Helicobacter pylori. Suitable antibacterial co-components which may be mentioned are, for example, mezlocillin, ampicillin, amoxicillin, cefalothin, cefoxitin, cefotaxim, imipenem, gentamycin, amikacin, eryth-

romycin, ciprofloxacin, metronidazole, clarithromycin, azithromycin and combinations thereof (for example clarithromycin + metronidazole).

Pharmacology

[0036] The excellent gastric protective action and the gastric acid secretion-inhibiting action of the compounds according to the invention can be demonstrated in investigations on animal experimental models. The compounds according to the invention investigated in the model mentioned below have been provided with numbers which correspond to the numbers of these compounds in the examples.

Tasting of the secretion-inhibiting action on the perfused rat stomach

[0037] In Table A which follows, the influence of the compounds according to the invention on the pentagastrin-stmulated acid secretion of the perfused rat stomach after intravenous administration in vivo is shown.

Table A

No.	Dose (μmol/kg) i.v.	Inhibition of acid secretion (%)
1	3	100

Methodology

[0038] The abdomen of anesthetized rats (CD rat, female, 200-250 g; 1.5 g/kg i.m. urethane) was opened after tracheotomy by a median upper abdominal incision and a PVC catheter was fixed transorally in the esophagus and another via the pylorus such that the ends of the tube just projected into the gastric lumen. The catheter leading from the pylorus led outwards into the right abdominal wall through a side opening.

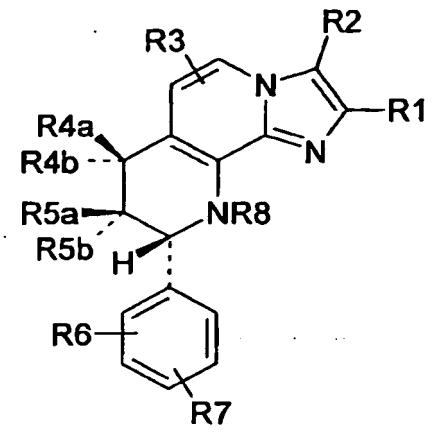
[0039] After thorough rinsing (about 50-100 ml), warm (37°C) physiological NaCl solution was continuously passed through the stomach (0.5 ml/min, pH 6.8-6.9; Braun-Unita 1). The pH (pH meter 632, glass electrode EA 147; ϕ = 5 mm, Metrohm) and, by titration with a freshly prepared 0.01 N NaOH solution to pH 7 (Dosimat 665 Metrohm), the secreted HCl were determined in the affluent in each case collected at an interval of 15 minutes.

[0040] The gastric secretion was stimulated by continuous infusion of 1 μg/kg (= 1.65 ml/h) of i.v. pentagastrin (left femoral vein) about 30 min after the end of the operation (i.e. after determination of 2 preliminary fractions). The substances to be tested were administered intravenously in a 1 ml/kg liquid volume 60 min after the start of the continuous pentagastrin infusion.

[0041] The body temperature of the animals was kept at a constant 37.8-38°C by infrared irradiation and heat pads (automatic, stepless control by means of a rectal temperature sensor).

Claims

1. A compound of the formula I



(I)

in which

R1 is 1-4C-alkyl,
R2 is 1-4C-alkyl,
R3 is hydrogen,

one of the substituents R4a and R4b is hydrogen and the other is R4'
where

R4' is $-O-(CH_2)_m-S(O)_n-R9$,

in which

R9 is 1-4C-alkyl,
m is the number 2 or 3 and
n is the number 0, 1 or 2,

one of the substituents R5a and R5b is hydrogen and the other is hydroxyl,

R6 is hydrogen,
R7 is hydrogen and
R8 is hydrogen,

and its salts.

2. A compound I as claimed in claim 1 in which R5b is hydrogen.

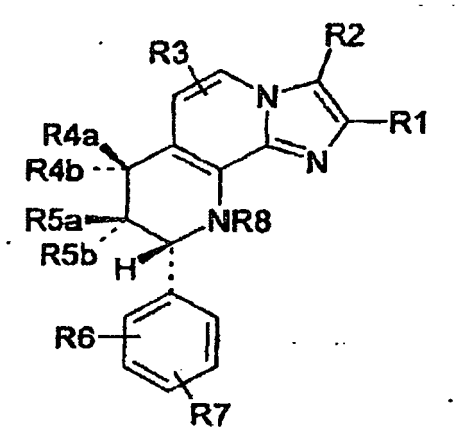
3. A compound I as claimed in claim 1 in which R5b is hydrogen and R4a is hydrogen.

4. A medicament comprising a compound as claimed in claim 1 and/or a pharmacologically acceptable salt thereof together with customary pharmaceutical auxiliaries and/or excipients.

5. The use of compounds as claimed in claim 1 and their pharmacologically acceptable salts for preparing medicaments for the prevention and treatment of gastrointestinal disorders.

Patentansprüche

1. Verbindungen der Formel I



(I)

worin

R1 1-4C-Alkyl bedeutet,
R2 1-4C-Alkyl bedeutet,
R3 Wasserstoff bedeutet,

einer der Substituenten R4a und R4b Wasserstoff und der andere R4' bedeutet,
wobei

R4' $-O-(CH_2)_m-S(O)_n-R9$ bedeutet,

worin

R9 1-4C-Alkyl bedeutet,
m die Zahl 2 oder 3 bedeutet und
n die Zahl 0, 1 oder 2 bedeutet,

einer der Substituenten R5a und R5b Wasserstoff und der andere Hydroxy bedeutet,

R6 Wasserstoff bedeutet,
R7 Wasserstoff bedeutet und
R8 Wasserstoff bedeutet

und ihre Salze.

2. Verbindungen I nach Anspruch 1, in denen R5b Wasserstoff bedeutet.

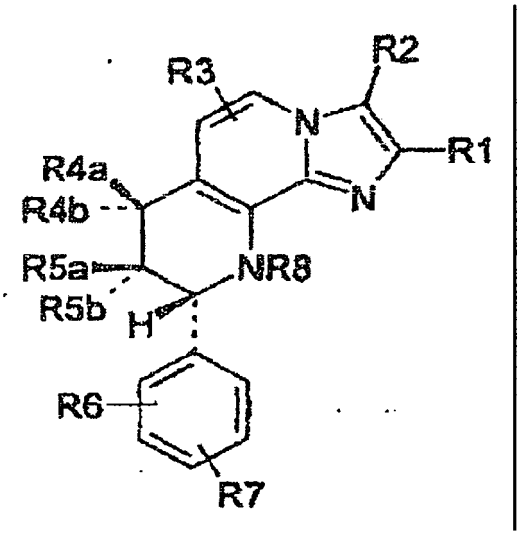
3. Verbindungen I nach Anspruch 1, in denen R5b Wasserstoff und R4a Wasserstoff bedeutet.

4. Arzneimittel enthaltend eine Verbindung nach Anspruch 1 und/oder ein pharmakologisch verträgliches Salz davon zusammen mit üblichen pharmazeutischen Hilfs- und/oder Trägerstoffen.

5. Verwendung von Verbindungen nach Anspruch 1 und ihren pharmakologisch verträglichen Salzen zur Herstellung von Arzneimitteln für die Verhütung und Behandlung gastrointestinaler Krankheiten.

Revendications

1. Composé de formule I



(I)

dans lequel

R1 est un alkyle en C_{1-4},
R2 est un alkyle en C_{1-4},
R3 est un hydrogène,
un des substituants R4a et R4b est un hydrogène et l'autre est R4'

où

R4' est $-O-(CH_2)_m-S(O)_n-R9$,

où

R9 est un alkyle en C_{1-4},
m est le nombre 2 ou 3 et
n est le nombre 0, 1 ou 2,
un des substituants R5a et R5b est un hydrogène et l'autre est un hydroxyle,
R6 est un hydrogène,
R7 est un hydrogène et
R8 est un hydrogène,
et ses sels.

2. Composé I selon la revendication 1 dans lequel R5b est un hydrogène.

3. Composé I selon la revendication 1 dans lequel R5b est un hydrogène et R4a est un hydrogène.

4. Médicament comprenant un composé selon la revendication 1 et/ou un sel pharmacologiquement acceptable de celui-ci conjointement avec des auxiliaires et/ou excipients pharmaceutiques usuels.

5. Utilisation de composés selon la revendication 1 et leurs sels pharmacologiquement acceptables pour préparer des médicaments pour la prévention et le traitement de troubles gastro-intestinaux.

REFERENCES CITED IN THE DESCRIPTION

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- WO 9842707 A **[0002] [0015]**

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- **S. PATAI.** The Chemistry of Functional Groups. John Wiley and Sons (Interscience Publication, 1980, vol. 1, 539-608 **[0017]**